REMARKS

Claims 1-13, 15, 16 and 18-30 are pending in the application.

Claims 14 and 17 have been canceled.

Claims 1-9 and 18-29 have been withdrawn.

Claim 10 has been amended. Support for the amendment can be found in paragraph [0059].

No new matter has been added.

Rejections Under 35 USC § 103

The Examiner has maintained her rejections for obviousness over *Kirker-Head* and further in view of *Wikesjö* 2003. The Examiner provides extensive comments on pages 4-14 in support of her position, which we do not repeat here. It would seem, however, that they can be summarized by the Examiner's statement on page 12 of the Office Action that the prior art, taken in combination, would have made it obvious to a skilled artisan "to try to make a periodontal transplant containing a neurotrophic factor selected from the group consisting of BDNF." Applicants respectfully traverse.

Applicants first note that the Examiner states that because the claims no longer recite an absorbent material, *Wikesjö* is not as critical (Office Action, page 6). However, the Examiner continues: "Nevertheless, *Wikesjö* 2003 do[es] illustrate that in spite of some ankylosis and root resorption with the absorbent implant (polyclycolic acid-trimethylene carbonate membrane or PGA-TMC), that their implant resulted in substantial bone regeneration . . ." (Office Action, page 6) The Examiner also states "it is noted that *Kirker-Head* does not teach ankylosis" (Office action, page 9).

These statements appear to be hindsight and/or speculation, as the Examiner is apparently attributing the occurrence of ankylosis solely to the absorbent material. However, *Wikesjö* states that the ankylosis occurs in various carrier systems using rhBMP-2 or rhOP-1/BMP-7 (*Wikesjö*, 643, right column). Thus, in contrast to the Examiner's assumption, one of skill in the art would have no reason to think that the ankylosis was caused by the absorbent material of *Wikesjö*. Instead, it would seem that one of skill in the art would expect that the neurotrophic factor was the cause of the detrimental side-effect.

In fact, whether or not *Wikesjö* is cited in the rejection, it reflects the knowledge of one of skill in the art. Thus, one of skill in the art would still understand that the occurrence of ankylosis strongly suggests that a therapy using the claimed product would not be efficacious, and therefore, the skilled artisan would not be motivated to make the claimed product. In addition, the teachings of *Wikesjö* are not limited to the periodontal implant disclosed therein, and apply to "various carrier systems." Thus, the teachings of *Wikesjö* should not be limited to the specific implant tested therein.

Applicants further submit that the Examiner has improperly dismissed the statements of one of skill in the art, that is Dr. Kurihara. The Examiner is required to consider ***all*** rebuttal evidence presented by the Applicant. *In re Sullivan,* 498 F3d 1345, 84 USPQ2d 1034 (Fed. Cir. 2007). Specifically, Dr. Kurihara's Declaration indicates that from the data presented in the tables and Figure 7 of *Wikesjö*, there was 100% ankylosis and root resorption rather than cementum regeneration (Declaration, page 2). *Wikesjö* itself states that the cementum "often merged with ankylotic bone in supraalveolar periodontal defects implanted with rhBMP-2/ACS" (*Wikesjö* 643, col. 2, lines 2-5). However, the Examiner has ignored Dr. Kurihara's characterization of the data as well as the teachings of *Wikesjö* itself to arrive at her conclusions and states "Applicants present only argument, without any evidence that one of skill in the art would understand periodontal tissue regeneration as excluding ankylosis." This is clearly a wrong conclusion because Dr. Kurihara ***is*** a skilled artisan, as evidenced by his curriculum vitae which was submitted at the same time as his Declaration. Dr. Kurihara's statements as to the understanding of a skilled artisan should therefore be given proper weight.

To assist the Examiner in understanding what was considered to be the knowledge of one skilled in the art at the time the invention was made in September of 2003 and to assist the Examiner to avoid using hindsight, Dr. Kurihara has provided a second Declaration that specifically sets forth the understanding of "one of skill in the art" at that time. In particular, Dr. Kurihara states that periodontal tissue was understood to consist of the supporting tissues of the tooth (gingival, periodontal ligament, cementum and alveolar bone). He notes that the cementum is a mineralized tissue, covering the entire root surface of the tooth and provides an anchorage site of the periodontal ligament fibers on the tooth.

Dr. Kurihara also states that the destruction of periodontal tissue occurs when interaction between bacteria in dental plaque and host defence reactions becomes unstable. There are several histological features that are associated with this, such as (1) marked apical migration and lateral extension of junctional epithelium, with areas of ulcefration; (2) loss of connective tissue attachment, resulting in true periodontal pocket formation; (3) loss of alveolar bone and (4) extensive chronic inflammatory infiltrate in connective tissue.

With respect to ankylosis, Dr. Kurihara defines this as fusion of the cementum and alveolar bone with obliteration of the periodontal ligament. Ankylosis results in resorption of the root and its gradual replacement by bone tissue.

Lastly, Dr. Kurihara states that the complete periodontal tissue regeneration requires the attachment of periodontal ligament cells and fibers to the previously denuded root surface with new cementum formation, the formation of a functionally orientated fiber network emanating from the root and the coronal regrowth of the alveolar bone. According to Dr. Kurihara, current periodontal therapy almost never achieves the new attachment formation or bone regeneration.

Further to Dr. Kurihara's statements above, it would seem that the Examiner's statement that ankylosis is not taught in *Kirker-Head* is a mischaracterization of the actual teachings of the article. *Kirker-Head* refers to 16 articles in reference to periodontal regeneration, (Section 2.4.5), seven of which refer to ankylosis *in the abstract* of the article. Thus, the Examiner's statement regarding the teachings of a survey article which covers many different therapies, and

which does not address periodontal surgery in-depth, overstates the actual teachings of *Kirker-Head.*

Applicants have also included a copy of the *Wikesjö* 1999 reference (Wikesjö et al. (1999) "Periodontal Repair In Dogs: Effect Of Rhbmp-2 Concentration On Regeneration Of Alveolar Bone And Periodontal Attachment," *J. Clin. Periodontol* 26: 392-400) that was submitted as "Exhibit 2" in the March 16, 2009 amendment. This paper reports that ankylosis was observed when periodontal defects were implanted with BMP-2 in an absorbable collagen sponge carrier.

Applicants have further enclosed a copy of the *Takeda* et al. 2005 reference (Takeda et al. (2005) "Brain-Derived Neurotrophic Factor Enhances Periodontal Tissue Regeneration" *Tissue Engineering* 11:1618-1629). This reference shows that BDNF immersed in a collagen carrier (atelocollagen sponge) was shown to promote periodontal tissue regeneration. As the reference states on page 1627, first column, third full paragraph, "[i]t is noteworthy that ankylosis and epithelial down-growth were not observed in the BDNF group." In other words, the lack of ankylosis appears to be the direct result of the use of BDNF in place of BMP-2. Or stated conversely, a BMP-2/absorbable collagen sponge carrier, such as that used in the Kirker-Head reference, will produce ankylosis, whether or not the Kirker-Head review article addresses this aspect of BMP-2 treatment.

The Examiner makes a point of focusing on the statements in the instant Specification regarding PLGA. Applicants have the right, however, to claim less than what they have disclosed. Consequently, the evidence presented in the Declaration filed with the Response of August 24, 2009 should be considered.

In conclusion, the Examiner has not made a proper case of prima facie obviousness. Consequently, Applicants respectfully request removal of the rejections and allowance of the claims.

Conclusion

In view of the above, all of the claims are submitted as defining non-obvious, patentable subject matter. Removal of the rejections and allowance of the claims are respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Susan W. Gorman, Ph.D., Reg. No. 47,604 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

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Enclosures: Wikesjö et al. (1999) "Periodontal Repair In Dogs: Effect Of Rhbmp-2 Concentration On Regeneration Of Alveolar Bone And Periodontal Attachment," *J. Clin. Periodontol* 26: 392-400

Takeda et al. (2005) "Brain-Derived Neurotrophic Factor Enhances Periodontal Tissue Regeneration" *Tissue Engineering* 11:1618-1629